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Endodermal Sinus Tumors in the Head and Neck Region

P. Kusumakumari, MD, DCH,* N. Geetha, MD, DCH, Dip.NB, DM,
V.G. Chellam, MD, and M. Krishnan Nair, MD, FRCR

Extragonadal germ cell tumors of the head and neck region account for only 5% of all benign and malignant germ cell tumors. Endodermal sinus tumors (EST) of the head and neck region are rare. We report three patients with EST of head and neck region over a period of 10 years; the primary sites of tumor were orbit, maxillofacial region and retroauricular region. Histopathological examination revealed malignant teratoma with predominant endodermal sinus pattern in two, and pure EST in one patient. Serum alpha fetoprotein (AFP) was elevated in all three patients. Two patients had initial surgery but did not receive adjuvant chemotherapy, as the parents refused it. Partial remission was achieved in the other patient who received chemotherapy (cisplatin, bleomycin and vinblastin) and the patient died of infection after four courses of chemotherapy. Med. Pediatr. Oncol. 29:303–307, 1997.
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INTRODUCTION

Germ cell neoplasm in both gonadal and extragonadal sites constitutes a small but important group of childhood tumors. Teratomas are the most common extragonadal germ cell tumor in childhood and are most frequently benign. Occasionally these tumors may contain malignant components, e.g., endodermal sinus tumor or embryonal carcinoma. In order of frequency, the most common locations of these neoplasms are sacrococcygeal, mediastinal, intracranial, and retroperitoneal sites. Teratomas of the head and neck region have also been reported, the cervicothyroidal area being the most frequently involved site.

Germ cell tumors are benign or malignant growths within the gonads or extragonadal sites and are derived from primordial germ cells. Extragonadal germ cell tumors (EGCT) usually present in midline structures, but are occasionally found in other locations such as prostate bladder, stomach, and liver [1]. It has been suggested that EGCT arise either from misplaced totipotential cells of the blastula or morula stage of embryogenesis or from the abnormal migration of primordial germ cells from the ectoderm of the yolk sac to the gonadal region. Mistakes in localization might cause these migrating cells to come to rest in some near midline site, such as sacrococcygeal area, retroperitoneum, neck, or even the pineal region of brain. If a malignant transformation takes place in these wandering cells, then a germ cell malignancy is produced. The oral cavity, pharynx, orbit, and neck account for approximately 6% of all germ cell tumors and these tumors are almost always benign and noted at birth. Only a few cases of malignancy have been previously reported in these sites. The purpose of this report is to document our experience with three malignant germ cell tumors originating in the head and neck region.

Case I

A 6-month-old female child was brought in October 1984 with the complaints of squinting and swelling of left eye of 2 months duration. Patient also had epistaxis. On examination she had proptosis, edema of lids and chemosis of left eye. Movements of left eye were limited. All other systems were within normal limits. Serum alpha foetoprotein was elevated. Computerised tomographic scan (CT scan) of the head showed a large tumor in the orbit extending into the ethmoid and downwards into the maxilla. There was no evidence of metastatic disease elsewhere. Orbital exenteration and removal of the mass was done. Histopathology was endodermal sinus tumor (no teratomatous elements were seen). Patient was advised to take chemotherapy but the parents refused. She died after 5 months.

Case II

A 1.5-year-old boy was brought in February 1985 with swelling in the palate of 5 months duration. Patient had feeding difficulties also for the last 2 months. Examination revealed an undernourished child with a growth in the palate extending anteriorly up to the alveo-

Regional Cancer Center, Trivandrum, Kerala, India.

*Correspondence to: P. Kusumakumari, Division of Paediatric Oncology, Regional Cancer Center, Trivandrum, Kerala, India.

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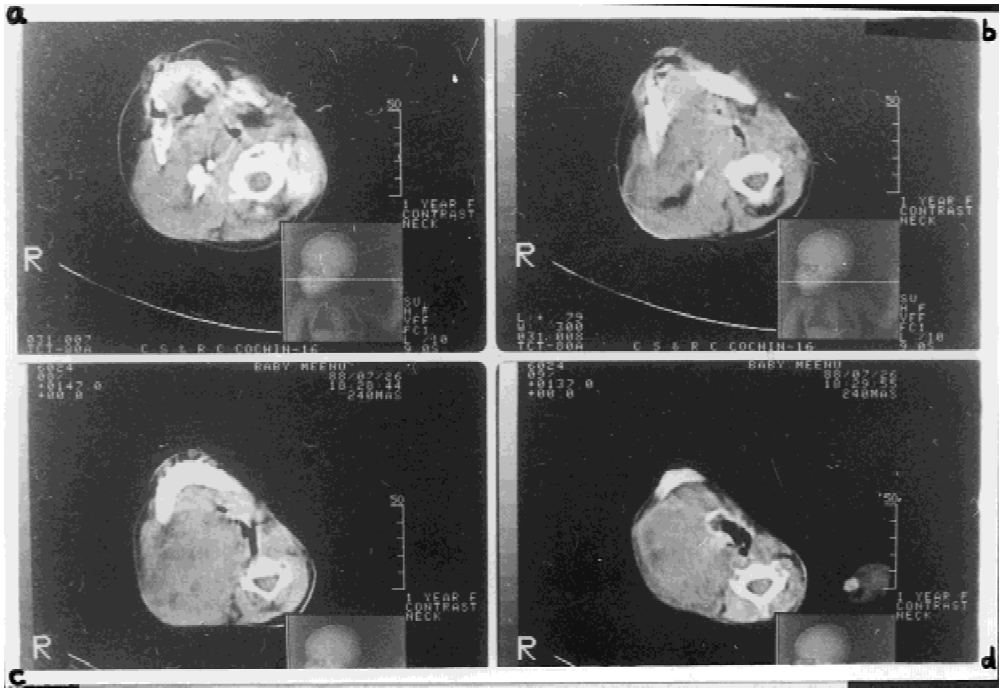

Fig. 1. Serial CT scan of case 3 showing a huge mass destroying the mandible, lower border of petrous part of temporal bone and pterygoid plates and partial compression of nasopharynx and trachea.

lus and posteriorly up to the nasopharynx. Other systems were within normal limits. Investigations revealed no evidence of metastasis. Surgical debulking was done and the histopathology was teratoma with predominant pattern of endodermal sinus tumor. The child was started on chemotherapy with injections of vincristine, cyclophosphamide and actinomycin D but was lost for follow-up after the first course of treatment.

Case III

A 1-year-old girl was brought to us in July 1988 with swelling of right side of neck of 2 months duration, which was rapidly increasing in size. Her general condition was unremarkable. There was a huge swelling over the right side of the neck, pushing the ear lobe upwards and extending to the submandibular region inferiorly and zygoma anteriorly. The skin overlying the swelling was reddish, tense and shiny. She also had associated right lower motor neuron facial nerve palsy. All other systems were within normal limits. CT scan of the head showed a huge nonenhancing solid mass in the neck, extending upwards to reach the base of skull, producing destruction in the posterior part of the mandible, the lower border of the petrous part of the temporal bone and the pterygoid plates on right side and producing partial compression and narrowing of the nasopharynx and trachea (Figs. 1 and 2). All the metastatic work up was negative. Biopsy of the swelling showed evidence of teratoma with endodermal sinus pattern. The child was treated with injections of cisplatin, vinblastine and bleomycin (PVB regimen) and complete response was noted on clinical examination; however, serum alpha fetoprotein (AFP) was still elevated and the repeat CT scan showed residual disease. Salvage chemotherapy was planned but the patient died of infection in a local hospital.

DISCUSSION

Germ cell tumors in children are characterized by diverse clinical, pathological and prognostic features. For this reason, it is difficult to generalize the behavior of these tumors. Cases must be evaluated individually considering the age of the patient at diagnosis, the anatomic site and its histologic appearance.

Teratomas are the most common EGCT in childhood. The nasopharynx, oral cavity, orbit and cervicothyroidal region are the sites of extracranial head and neck teratomas. Regardless of location, teratomas can be composed of mature and immature tissue elements and some may contain frankly malignant components such as endodermal sinus tumor (EST). EST as a component of a mixed germ cell tumor or less frequently as the only representative tissue is the most common histological type in the head and neck region for this type of malignancy. The term EST was introduced by Teilum in 1959 to describe a germ cell neoplasm that occurred in ovaries and testes of infants and children [2]. EST is thought to arise from undifferentiated embryonal carcinoma through selected differentiation to vitelline tissue similar to that observed in the rat placenta. There are very few reports of extra-

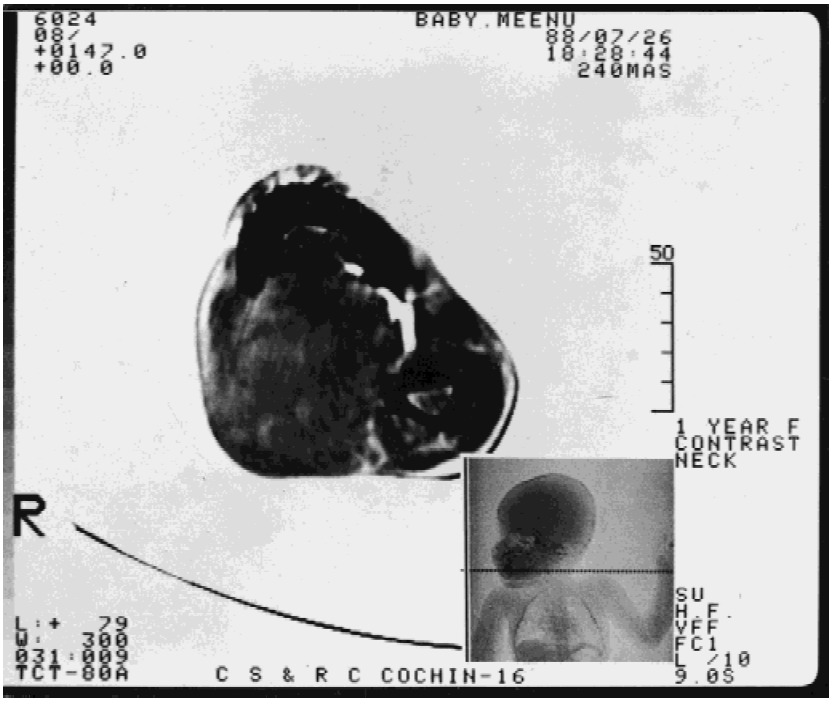

Fig. 2. An enlarged view of figure 1C.

cranial head and neck EST in the literature. Weedon and Musgrave [3] described a female infant who had EST in the maxillofacial area diagnosed at the age of 10 months, and she died one month later. Margo et al. [4] reported five cases of EST of orbit occurring in children between ages 3 months and 4 years. There were three cases of EST reported by Lack [5]; the tumors presented within the oropharynx, nasopharynx and floor of mouth. In the series of EST reported by Shehib et al. [6], two out of eleven cases had tumors in the head and neck region. Soft tissues of the facial and temperomastoidal regions were the sites of four EST studied by Dehner et al. [7]. Maxillofacial region and temporal region were the primary sites of disease reported by Nair et al. [8] and Kebudi et al. [9]. Orbit, maxilla and retroauricular regions were the sites of tumor in our study. Two of our cases (cases II and III) had mixed germ cell tumors with a prominent EST component, whereas case I showed pure EST elements. Lack [5] has reported the tendency of cervical teratoma to involve the right side of the neck and our patient also (case III) had the tumor on the right side. Alkemade [10], in a review of the literature, found that the left eye was affected more frequently than the right eye in orbital teratomas, which was also seen in our case. The reasons for these predilections are unclear.

A number of theories have been proposed to explain the origin of germ cell tumors. Primordial germ cells first become identifiable among endodermal cells of yolk sac of the 4-week embryo and migrate during embryogenesis along dorsal mesentery to the embryonic gonads. Most germ cell tumors (GCT) occur along the midline of the body. Some may occur away from the midline. Gonadal GCT are generally believed to arise from primodial germ cells within the ovary or testes. EGCT possibly arise from primordial germ cells that migrated improperly during embryonic development or they may originate from undifferentiated pleuripotent embryonic or extraembryonic cells that have escaped the influence of primary developmental organizers. More recently, it has been suggested that germ cells are present in apparently ectopic sites in all healthy persons, having been distributed widely during normal embryogenesis to liver, thymus, bone marrow and brain, and that these cells may provide important regulatory functions [11]. Hoffner et al. [12] reported data to support multiple genetic origins for ovarian germ cell tumors, namely, meiosis I nondisjunction, meiosis II nondisjunction, endoreduplication of a haploid ovum, mitotic proliferation of a premeiotic germ cell and the fusion of two haploid ova. Their further studies suggested that EGCT and testicular GCTs do not arise by a meiosis I or II error or by endoreduplication; rather, they arise mitotically from either a somatic or a germ cell. The identical nature of the tumor chromosomes and the host including chromosomal centromeric heteromorphisms and DNA markers, indicate that the tumor cells are genetically indistinguishable from the host cells.

The histopathological appearance of EST is quite variable. Four basic patterns have been described, namely pseudopapillary or festoon, reticular, polyvesicular vitelline, and solid [13]. Pseudopapillary pattern is the classic

pattern often associated with the formation of Schiller Duval bodies.

These tumors secrete AFP. Several investigators have used immunofluorescent techniques to localize AFP synthesis in EST samples [14]. The serum levels of AFP may be used as a tumor marker to help in the diagnosis and follow-up of these tumors. The three cases in our study had morphologic and functional characteristics of EST. EST was identifiable in the background of other teratomatous elements in two patients (cases 2 and 3), and in one patient (case 1) no other elements were found. The classic Schiller Duval bodies were present in all three patients. The serum AFP was also elevated in all these patients.

There are conflicting reports concerning outcome of children with EGCT. Kurman and Norris [15] reported EST of ovary treated with surgical excision, and 89% of patients eventually developed metastases and died. The prognosis for malignant germ cell tumors improved considerably with the introduction of cisplatin-based chemotherapeutic regimens. Most of these studies were initially conducted in testicular tumors and then also extended for treating other germ cell tumors. Evidence suggests that some EGCT are distinct clinically and pathologically from testicular primary tumors and that they have a different natural history and therefore require a specific treatment. Although some authors have reported equivalent response rates to chemotherapy for patients with EGCT compared with primary gonadal germ cell tumors, most have suggested that survival is poorer particularly for patients with nonseminomatous EGCT.

Many investigators assign all patients with extragonadal nonseminomatous germ cell tumors to high risk treatment protocols, believing that an extragonadal presentation is an independent adverse prognostic factor. Hawkins et al. [16], in their study of 89 cases of nongerminomatous malignant germ cell tumors in children, confirmed that testicular and ovarian tumors in children have a better prognosis and that site of origin is the single most important prognostic criterion. EGCT in the head and neck region is usually unresectable at diagnosis and is associated with worse prognosis. The disease-free survival was 49% at 4 years in 93 children treated with injection vinblastine, bleomycin, cisplatin, dactinomycin, and cyclophosphamide in the series reported by Ablin et al. [17]. This relatively low survival rate was attributed to the low dosages of cyclophosphamide and cisplatin. At St. Jude Children Research Hospital, 51 children with malignant germ cell tumors were given either vincristine, actinomycin, cyclophosphamide (VAC) or cisplatin, vinblastine, bleomycin (PVB) and or radiotherapy, the survival rate was 73% [18]. Using high-dose vincristine, actinomycin, cyclophosphamide (VAC) or bleomycin, etoposide, cisplatin (BEP), the United Kingdom Children's Cancer Study Group (UKCCSG) could achieve a disease-free survival of 85% [19]. All these studies included children with both gonadal and extragonadal tumors.

Israel et al. [20] studied 38 patients with EGCT treated with high-dose cisplatin-based chemotherapy. Complete response was achieved in only 41% (12/29) of patients with extragonadal nonseminomatous germ cell tumors and only four are alive and free of disease. Their study concluded that patients with extragonadal nongerminomatous germ cell tumor have a relatively poor prognosis when compared with primary testicular or ovarian tumors. In the series reported by Garnick et al. [21], 15 patients with EGCT were treated with vinblastine bleomycin and cisplatin followed by tumor-reductive surgery. Cyclophosphamide and doxorubicin were given after surgery. Ten patients (67%) achieved complete remission and only four patients are disease-free for a median period of 40 months. Thus, some therapeutic strategies may be inadequate in the treatment of patients with EGCT.

Only partial response was achieved after four courses of PVB in our patient (case 3) who did not have initial surgery. Patient 1 did not receive any chemotherapy and patient 2 was lost to follow-up after one course of VAC. Hence, it is difficult to comment about the treatment outcome in our patients.

In conclusion, even though rare, EST do occur in the head and neck region, and the affected patients must be treated with a curative intent. Patients with resectable tumors should undergo surgery. Adjuvant chemotherapy is indicated in all cases. A combination of cisplatin, etoposide and bleomycin used in treating poor prognosis gonadal germ cell tumor may improve the outcome of patients with EGCT. Patients with residual active disease require salvage chemotherapy. Addition of radiotherapy may be beneficial in surgically inaccessible regions. Most of the reported series have a limited number of cases of EGCT of head and neck region. Hence, the optimum treatment of these tumors has yet to be defined.

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